

## Prenatal PCB Exposure, the Corpus Callosum, and Response Inhibition

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The present study reports the association between prenatal exposure to polychlorinated biphenyls (PCBs), the corpus callosum, and response inhibition in children who are 4.5 years old. Children ( $n = 189$ ) enrolled in the Oswego study were tested using a continuous performance test. We measured (square millimeters) the splenium of the corpus callosum, a pathway implicated in the regulation of response inhibition, using magnetic resonance imaging. Results indicated a dose-dependent association between cord blood PCBs and errors of commission. Splenium size but not other brain areas predicted errors of commission ( $r^2 = 0.20$ ), with smaller size associated with more errors of commission. There was an interaction between splenium size and PCB exposure. The smaller the splenium, the larger the association between PCBs and errors of commission. If the association between PCBs and response inhibition is indeed causal, then children with suboptimal development of the splenium are particularly vulnerable to these effects. These data await replication. **Key words:** corpus callosum, impulsivity, inhibition, PCBs, polychlorinated biphenyls, splenium. *Environ Health Perspect* 111:1670–1677 (2003). doi:10.1289/ehp.6173 available via <http://dx.doi.org/> [Online 16 June 2003]

Response inhibition is a behavioral process characterized by active termination of prepotent, ongoing, or otherwise routinized behaviors (Barkley 1997). As such, response inhibition is crucial to the ongoing regulation of behavior—the ability to change behavior in response to changing environmental contingencies, to withhold or delay responding when appropriate, and to inhibit responses that are no longer relevant or adaptive in new contexts. Response inhibition is a key behavioral process for the successful completion of many tasks such as the continuous performance task (Losier et al. 1996), fixed-interval (FI) schedules of reinforcement (Darcheville et al. 1992; Rice 1997; Sagvolden et al. 1998), and delayed-response paradigms (Rice 1999a). At a more molar level of behavioral analysis, Barkley (1997) has theorized that response inhibition is required for several downstream behavioral processes, including working memory, regulation of affect, and performance of rule-governed behavior. This is in large part because disruptive or potentially competing behaviors must be inhibited during the execution of these processes. Not surprisingly, response inhibition is frequently impaired in children with attention-deficit hyperactivity disorder (ADHD) (Klorman et al. 1991; Losier et al. 1996; Mota and Schachar 2000; Sagvolden et al. 1998; Schachar and Logan 1990; Schachar and Tannock 1993) and in animal models of this disorder (Berger and Sagvolden 1998; Sagvolden et al. 1992).

Evidence suggests that common neurotoxins such as lead and polychlorinated biphenyls (PCBs) impair response inhibition in animals. Lead, in particular, has been reliably associated with impaired response inhibition in

FI schedules of reinforcement (Cory-Slechta and Pokora 1991; Cory-Slechta et al. 2002), where low levels of lead cause rats to respond far in excess of the requirements of the reinforcement schedule. PCBs, a ubiquitous organochlorine contaminant in the environment, have also been associated with impaired response inhibition in rats in several studies (Berger 2001; Lillenthal et al. 1990). Possibly owing to differences in dosing and methodology, however, these results have not always been detected (Bushnell 2002; Holene et al. 1999). Most relevant to humans, however, is the work conducted with nonhuman primates, whose behavioral and physiologic characteristics are much closer to humans than are those of rats. Mele et al. (1986) showed that monkeys exposed to PCBs *in utero* responded excessively and inappropriately after reinforcement omission during schedule-controlled behavior. Even more pertinent is the work of Rice (1997, 1999b), who demonstrated PCB-induced impairments in response inhibition in monkeys on both FI and differential reinforcements of low rates. In each task, the ability to withhold responses during temporal delays was a key component of learning the task. However, PCB-exposed monkeys responded excessively and inappropriately relative to control monkeys, even when premature responses resulted in delay of reinforcement.

Despite the heuristic value of these data, few studies in the epidemiologic literature have examined response inhibition in PCB-exposed children, let alone the neuroanatomic structures correlated with these behaviors. Of those studies where response inhibition was clearly necessary for the children to complete the tasks, none has analyzed the data in a way that would isolate the variable that specifically

reflects this process (i.e., errors of commission) (Grandjean et al. 2001; Jacobson et al. 1992).

Other major PCB cohort studies, including North Carolina, Dutch, and German cohorts, have not reported any investigations of response inhibition. Rather, these studies appear to have bypassed such domain-specific questions in favor of global cognitive tests and/or intelligence quotient (IQ) (Patandin et al. 1999; Rogan and Gladen 1992; Walkowiak et al. 2001). On the basis of all the above, it is clear that response inhibition is important yet, paradoxically, has received scant attention as an outcome measure in the human PCB literature. The present study was designed to address this deficiency. Children enrolled in the Oswego study were assessed using the Michigan Catch-the-Cat test, a variant of a continuous performance test (CPT), at 4.5 years old. The hypothesis being tested was that prenatal PCB exposure would impair response inhibition, specifically in the form of increased errors of commission. In addition, magnetic resonance imaging (MRI) scans were performed in the least exposed and most exposed children. The goal was to determine if any putative PCB-related deficits in response inhibition were associated with the morphometric changes in the posterior corpus callosum typically seen in disorders associated with impulse behavior, such as ADHD (Hynd et al. 1991; Semrud-Clikeman et al. 1994) and resistance to thyroid hormone (Hauser et al. 1997).

### Methods

**Participants.** Subjects described in the present report are enrolled in the Oswego Newborn and Infant Development Project, a prospective, longitudinal study of the neurobehavioral correlates of PCBs in mothers and children in the Great Lakes region (Lonky et al. 1996). The children of the maternal participants were recruited at birth from 1991 through 1994; prenatal exposure and demographic and

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control data were collected at time of enrollment. The sampling methodology and demographic and exposure characteristics of this cohort have been published in detail previously (Darvill et al. 2000; Lonky et al. 1996; Stewart et al. 1999, 2000, 2003). Briefly, subjects represent predominantly white, lower- to middle-class families from the local community. Approximately half the participants reported consuming Lake Ontario fish (Lonky et al. 1996). Key demographic characteristics of the sample are shown in Table 1. Tissue levels of the principle contaminants are shown in Table 2.

Of the original 293 subjects with valid exposure information (Stewart et al. 2000), 230 chose to have their children participate in the longitudinal phase (6 months and beyond). Of these 230 subjects, 33 were either lost to follow-up or were unable to meet the schedule for testing at 4.5 years. Thus, 197 children were tested at 4.5 years old. Data for eight of these children were lost because of computer failure. Analysis of the pattern of attrition for potential sampling bias at the 4.5-year testing protocol has been reported (Stewart et al. 2003). Results suggested that some of the less educated families with children who are at greater risk for performing poorly on earlier developmental assessments had dropped from the sample. However, subjects who dropped from the study were no more or less exposed to total PCBs ( $p = 0.19$ ), highly chlorinated PCBs ( $p = 0.824$ ), methylmercury (MeHg;  $p = 0.45$ ), or other key contaminants than were those who remained. Thus, the pattern of attrition is related to social and demographic indices, but not to contaminant exposure. It is unlikely that differences in the performance of PCB-exposed children on the Catch-the-Cat test are caused by sampling bias.

**Classification of exposure.** Immediately after birth, a sample of umbilical cord blood was obtained from participants ( $n = 293$ ) for analysis of PCBs by capillary column gas chromatography. Sample collection and analysis methods have been described (Stewart et al. 1999). In addition, maternal hair samples

**Table 1.** Key sample demographics for subjects at 4.5 years old.

Characteristics	Values
Socioeconomic status <sup>a</sup> (mean ± SD)	49.83 ± 13.43
Lower class (%)	42
Middle class (%)	55
Upper class (%)	3
Mother married (%)	64
Maternal age (years) <sup>a</sup> (mean ± SD)	32 ± 5.13
Maternal IQ <sup>aa</sup> (mean ± SD)	94.71 ± 14.29
Child racial characteristics	
White (%)	99
African American (%)	0.5
Latin American (%)	0.5
Child sex (% male)	45

<sup>a</sup>Hollingshead two-factor index (Hollingshead and Redlich 1958). <sup>aa</sup>Peabody picture vocabulary test.

were collected within 24 hr of birth for analysis for MeHg. Prenatal lead levels were measured in cord blood (Stewart et al. 2003). Postnatal lead levels were measured when the children were between 2 and 4 years old (Table 3). As described previously (Stewart et al. 1999, 2000, 2003), we used the most persistent and highly chlorinated PCB congeners (hepta-, octa-, and nonachlorinated biphenyl homologues; sum of congener peaks 170+190, 172, 174, 177, 179, 180, 183, 185, 187+181, 194, 195, 199, 203+196, 206) as a measure of cumulative PCB exposure in cord blood. Because a large number of samples ( $n = 173$  out of 293) had nondetectable highly chlorinated PCBs, the data did not approximate a normal distribution and could not be corrected by log transformation. Because the normality assumptions of a regression model would be violated, PCB cord data were treated in an ordinal rather than interval manner and analysis of variance was used in lieu of regression. The distribution of highly chlorinated PCBs (ng/g wet weight), measured in all subjects at birth, was divided into four groups. These groups consisted of subjects with nondetectable levels of highly chlorinated PCBs in cord blood ( $n = 173$ ) and those in the lower ( $n = 40$ ), middle ( $n = 40$ ), and upper ( $n = 40$ ) tertiles of the distribution of subjects with detectable levels. Absolute PCB levels (ng/g) that corresponded to these cutoffs were 0 (nondetectable), > 0.001 (low), > 0.02 (medium), and > 0.09 (high) ng/g PCB. Tertiles were constructed from the original distributions (measured at the time of birth for the 293 subjects), and not the distribution that existed at the time of the Catch-the-Cat test ( $n = 197$  tested). Thus, the sample sizes for subjects tested using the Catch-the-Cat test in the present study reflect unequal  $n$  values due to subject attrition and/or unavailability for testing. For the present report, data were available for 189 subjects with both PCB exposure and Catch-the-Cat performance data. The sample sizes for the Catch-the-Cat test are as follows: nondetectable PCB ( $n = 112$ ), low exposure ( $n = 24$ ), medium exposure ( $n = 27$ ), high exposure ( $n = 26$ ).

**Testing procedure.** In most instances, assessment took place in our laboratory at the

State University of New York at Oswego. Occasionally, limitations related to the mother's schedule or transportation required that testing occur in the child's home. Where home assessments were conducted, a second member of the behavioral assessment staff occupied the child's mother and siblings in a separate room. There were three pairs of principal examiners. On average, the visits required approximately 90 min; the McCarthy Scales of Children Abilities (Stewart et al. 2003) was administered first, followed by the Catch-the-Cat test.

**Continuous performance testing.** A version of the CPT called the Michigan Catch-the-Cat Test (version 1.2; Jacobson et al. 1992) was employed in the present study. The program was run on a laptop personal computer (IBM PS/2 model CL57) that included an attachable joystick device for subject input. The CPT consisted of a computerized image of a house with three windows, where a stimulus (an apple, butterfly, or cat) appeared. The cat was the target stimulus, and the other two stimuli were nontargets. The test provided a total of 126 stimulus presentations, divided into three consecutive blocks of 42 stimulus presentations each. During each block, the three stimuli had an equal chance (one-third or 33%) of appearing and were displayed in one of the three "windows" (random location) for a stimulus duration of 500 msec. Stimuli were presented on a variable interval (VI-5) schedule (mean interstimulus interval = 4.87 sec; SD = 1.6 sec; range = 3–11 sec). No more than one stimulus could appear at a time, and the number of presentations of each stimulus was restricted such that each was presented 14 times per testing block. Each child was instructed to "catch the cat" by pushing the button on the joystick as fast as possible when the target (cat) appeared, but not when nontargets (apple or butterfly) appeared. A response was recorded as "correct" when the child's response to the target (cat) stimulus occurred between 200 and 3,000 msec after the stimulus onset. A response made any time after this time window, up to and including nontarget stimuli (apple or butterfly), was considered an error of commission. A response recorded before 200 msec after target onset was also considered an error of commission. This is

**Table 2.** Contaminant levels in cord blood, breast milk, and maternal hair for 25th, 50th, and 75th quartiles.

Contaminant	25th	50th	75th
Breast milk total PCBs ( $n = 86$ )	87.00 ng/g lipid 2.75 ng/g wet	153.00 ng/g lipid 5.03 ng/g wet	249.00 ng/g lipid 8.59 ng/g wet
Cord total PCBs ( $n = 293$ )	0.17 ng/g wet	0.52 ng/g wet	1.11 ng/g wet
Cord highly chlorinated PCBs ( $n = 293$ ) <sup>a</sup>	0.01 ng/g wet	0.05 ng/g wet	0.02 ng/g wet
Cord lead ( $n = 282$ )	1.00 µg/dL	1.70 µg/dL	2.00 µg/dL
Maternal hair Hg			
First half of pregnancy ( $n = 225$ )	0.40 ng/mg	0.50 ng/mg	0.60 ng/mg
Second half of pregnancy ( $n = 209$ )	0.40 ng/mg	0.50 ng/mg	0.70 ng/mg

Quartiles are presented for those values above the limit of detection.

<sup>a</sup>59% of the samples had nondetectable highly chlorinated PCBs.

consistent with the fact that reaction time to a stimulus during signal detection tasks with at least three alternative stimuli is no faster than 300–400 msec (Coren and Ward 1989). Therefore, for tests with sequential trials of stimuli, responses that occur before 200 msec

after target onset are actually initiated before the target onset, and not in response to the target itself. Before the actual test, a shape-learning exercise and trial (practice) run were implemented for each child, as described in the testing manual (not published). For each of the

three testing blocks, the computer generated the percent correct (percentage of responses to the target windows) and percent commission errors (percentage of responses to the nontarget windows). Total testing took approximately 12 min.

**Behavioral observations.** If the child failed to remain seated at any time during testing, the child was instructed to remain seated and the incident was recorded. Data for this variable were dichotomous.

**Child satisfaction rating.** Immediately after the CPT, each child was asked to report how he or she felt about performing the task. This was in response to Daly's findings (Daly 1992; Daly et al. 1989) that rats fed Lake Ontario fish were more reactive to negative events. The child was verbally asked the question "How much fun did you have doing this activity?" The child was given the opportunity to respond on a Likert scale containing five "smiley faces," ranging from extremely unhappy to extremely happy, and was instructed to circle one of the five faces. Children were helped to understand this through a relative validation process of relating the "smile" faces to specific activities that they liked, and "frown" faces to activities that they disliked.

**MRI testing.** Approximately 24 months after the last child was tested on the Catch-the-Cat test, funding became available to conduct MRI scans of 60 subjects in the project. Funding permitted scanning the brains of the 30 children most exposed to PCBs and 30 of those least exposed, matched on sex and handedness.

All subjects underwent a gradient echo volumetric scan using a 0.5 T MRI. A pilot scan in the transverse plane was used to position the sagittal grid parallel to the interhemispheric fissure. We used parameters for the scan that have been described in a previous study (Leonard et al. 1995). The following parameters were found to be optimal: (repetition time = 20 msec; echo time = 6 msec, 45° flip angle, field of view = 26 cm, 130 × 256 matrix, 7.9 min acquisition time). Ninety contiguous high-contrast thin (2 mm) sagittal images were obtained on each subject. The midsagittal slice was identified as the section containing a visible septum pellucidum, distinct thalamus, optic recess, and a patent cerebral aqueduct.

The images were prepared for measurement using Analyze (version 7.5.4) image processing program (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). The midsagittal slice from each subject was selected and coded. All identifying information on the films was deleted to eliminate cues to age, sex, and PCB exposure category. We modified the scheme used by Giedd et al. (1994) to divide the corpus callosum into six subregions. The corpus callosum was manually traced on the midsagittal slice. A horizontal line was

**Table 3.** Percent commission errors.

Covariates	Block 1	Block 2	Block 3
<b>Demographic</b>			
Maternal education	-0.063	-0.156**	-0.081
Paternal education	-0.073	-0.168**	-0.138*
Parity of child	-0.113*	-0.047	-0.128*
Socioeconomic status	-0.098*	-0.182*	-0.128*
Maternal IQ (Peabody picture vocabulary test)	-0.039	-0.066	-0.017
Maternal age	-0.070	-0.096*	-0.119*
Maternal height	-0.041	-0.077	-0.057
Paternal age	-0.095*	-0.128*	-0.098*
Paternal height	-0.032	-0.007	0.052
Paternal weight	-0.073	-0.020	0.077
HOME 12 months	-0.140**	-0.180**	-0.165**
HOME 54 months	-0.226***	-0.232***	-0.206***
Number years at same address	-0.056	-0.062	-0.055
Number years near Great Lakes	0.033	-0.022	-0.071
Maternal marital status	0.211***	0.199***	0.134*
Day care	-0.057	-0.018	0.053
Home care	-0.055	-0.030	-0.087
<b>Health/nutrition</b>			
Prepregnancy weight	0.142**	0.121*	0.129*
Weight gain during pregnancy	-0.026	-0.030	-0.083
Stress before pregnancy	0.052	0.038	0.112*
Stress first half pregnancy	-0.019	-0.073	-0.069
Stress second half pregnancy	-0.040	-0.032	-0.032
Maternal illness history	0.044	0.043	0.070
Obstetric optimality	-0.260***	-0.220***	-0.115*
Vitamins during pregnancy	-0.009	-0.054	-0.042
Prescription medications during pregnancy	-0.026	-0.069	0.024
Nonprescription medications during pregnancy	-0.001	-0.017	0.095*
Nutrition scale	0.070	0.109*	0.133*
<b>Infant birth characteristics</b>			
Child sex	-0.258***	-0.300***	-0.307***
Birth weight (g)	-0.083	-0.046	-0.029
Head circumference	0.005	0.009	0.016
Ballard: neuromuscular	-0.041	-0.060	0.016
Ballard: physical	-0.199***	-0.217***	-0.194***
Gestational age at birth	-0.070	-0.150**	-0.157**
Erythrocyte porphyrin (cord blood)	0.074	0.060	0.109*
<b>Substance use</b>			
Cigarettes/day	0.045	0.139*	0.119*
Second-hand smoke (hrs/day)	0.138*	0.200***	0.156**
Alcohol (no. drinks/day)	-0.081	-0.099*	-0.116*
Herbal tea (drinks/mo.)	-0.051	-0.023	-0.008
Decaffeinated coffee (drinks/month)	-0.016	-0.053	-0.083
Diet soda (drinks/month)	0.021	-0.069	-0.048
Decaffeinated soda (drinks/month)	0.074	0.051	0.043
Caffeinated beverages (drinks/month)	0.028	0.100*	0.177**
Child current medications	-0.037	-0.104*	-0.207***
<b>Non-PCB Contaminants</b>			
DDE	-0.017	-0.008	-0.006
Hexachlorobenzene	-0.057	-0.057	-0.070
Hg (first half pregnancy)	-0.015	-0.016	-0.062
Hg (second half pregnancy)	0.074	0.065	0.010
Lead (cord)	0.143**	0.075	0.069
Lead (postnatal)	0.158*	0.193**	0.039
Mirex	N/A	N/A	N/A
<b>Other</b>			
Examiner	0.131*	0.155**	0.217***
<b>Effect mediators</b>			
McCarthy General Cognitive Index	-0.233***	-0.258***	-0.202***
Corpus callosum (splenium; mm <sup>2</sup> )	-0.382***	-0.441***	-0.454***
Getting out of seat (yes/no)	0.390***	0.322***	0.200**

\* $p < 0.20$ ; \*\* $p < 0.05$ ; \*\*\* $p < 0.01$ .

drawn from the base of the splenium to the base of the genu. Vertical lines, perpendicular to the horizontal reference line, were drawn at the anterior aspect of the genu and posterior aspect of the splenium. The midpoint of the horizontal line between the two vertical reference lines was determined. A radial divider was placed at the midpoint of the horizontal reference line to divide the corpus callosum into six subregions: CC1 (genu), CC2, CC3, CC4, CC5, and CC6 (splenium). Area measurements (in square millimeters) were made within each of the six regions of interest. Although six subregions were measured, only the genu and the splenium (Figure 1) were considered in this analysis, because there is a literature base for these structures (Giedd et al. 1999; Hynd et al. 1991; Semrud-Clikeman et al. 1994). The midsagittal cerebral area was also determined by manually tracing the cerebrum.

**Statistical methodology. Treatment of potential confounders.** Data for potential confounding variables were collected from psychometric tests, hospital records, structured interviews, and repeated assessments of the home environment [e.g., Home Observation Measure of the Environment (HOME Inventory measures)] when the children were 12 and 54 months old. Details regarding the collection of these data are described elsewhere (Darvill et al. 2000; Lonky et al. 1996; Stewart et al. 2000, 2003). Table 3 presents a list of the potentially confounding variables considered in the present analysis.

The decision rule for the inclusion of covariates in the present study is consistent with that employed previously (Darvill et al. 2000; Stewart et al. 2000, 2003), as well as others (Jacobson and Jacobson 1996). Any potential confounding variables even marginally related ( $p < 0.20$ ) to performance served as covariates in all analyses. In cases where MeHg was used as a covariate for the PCB analysis, subjects with missing MeHg data were assigned an MeHg value equal to the group mean of the MeHg levels of their PCB exposure group. With respect to the two HOME measures at 12 and 54 months, both were correlated with the Catch-the-Cat test, and both were eligible for inclusion. Relationships between covariates and outcome were first determined through single-pass, bivariate correlations. With this approach, all covariates related at  $p < 0.20$  to outcome were included in the final model. Data for each testing block were statistically adjusted by the included covariates.

**Statistical treatment of the predictor variable (PCBs).** A  $4 \times 3$  repeated-measures analysis of variance was conducted with a linear  $F$ -test for PCB exposure as the between-subjects variable (four levels) and testing block as the within-subjects variable (three levels), while controlling for relevant covariates.

This permitted assessment of the main effect of PCB exposure, the main effect of testing block, and any PCB  $\times$  testing block interaction. This analysis permitted the test of the hypothesis that a linear, dose-dependent association between cord-blood PCBs and CPT performance existed. Apparent departures from linearity were assessed via Sidak reversals at high  $\alpha$  ( $p < 0.20$ ), as recommended by Braver and Sheets (1993). A linear association between cord blood PCBs and CPT performance was regarded as significant only if *a*) the linear term for cord blood PCBs was significantly ( $p < 0.05$ ) related to CPT performance after control for potentially confounding variables at  $p < 0.20$  and *b*) there were no statistically significant departures from linearity using a Sidak reversal test with a liberal  $\alpha$  of  $p < 0.20$ . Two-tailed significance tests ( $\alpha = 0.05$ ) were used.

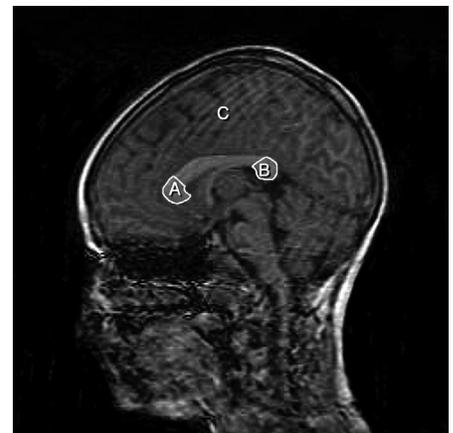
**Treatment of effect mediators.** Three variables, the McCarthy General Cognitive Index at 4.5 years (Stewart et al. 2003), the volume (square millimeters) of the splenium of the corpus callosum (for a subsample of 60 subjects), and failure to remain seated (yes/no) during testing, may be considered effect mediators (Baron and Kenny 1986). The variables cannot be considered potential confounders in the traditional sense, because they represent physiologic or behavioral characteristics of the child, and not independent influences on their behavior. Therefore, PCBs may affect them, and in turn these variables may affect outcome on the CPT. To test for mediation, these variables were used as covariates only after a covariate-controlled, significant association between PCBs and the CPT was first demonstrated. If the association between PCBs and CPT performance significantly changed after the use of these variables as covariates, the variable was considered a mediator (Gump et al. 1998). In all analyses, all other potential covariates (i.e., nonmediators, confounders) remained in the model.

## Results

**CPT parameters.** Average percentage of correct responses for the entire sample declined across the three testing blocks [percent correct = 64.6%, 58.65%, and 53.65%, respectively; testing block  $F(2,376) = 19.67$ ,  $p < 0.0009$ ]. In addition, percentage of errors of commission increased across the three testing blocks [23.21%, 35.9%, 39.1%;  $F(2,376) = 6.25$ ,  $p = 0.002$ ]. There was no difference in the percentage of correct in PCB-exposed children relative to lesser-exposed children [ $F(1,177) = 0.40$ ,  $p = 0.527$ ]. However, children with higher levels of PCB exposure showed significantly greater percentages of errors of commission, especially during the latter testing blocks [PCB  $\times$  testing block interaction:  $F(2,370) = 5.24$ ,  $p = 0.006$ ; Figure 2A,B].

In fact, the overall increase in percent errors of commission across the testing blocks was entirely due to PCB-exposed children, whereas children who were less exposed maintained consistently lower and unchanged errors of commission throughout testing (Figure 2B). For the least exposed children (nondetectable levels), percent commission errors across the three testing blocks were stable at 32.3%, 33.8%, and 33.8%, respectively [block:  $F(2,222) = 0.14$ ,  $p = 0.871$ ]. For children with detectable, but low levels of exposure, percent commission errors across the three blocks were 28%, 35.3%, and 38.4% [block:  $F(2,46) = 3.13$ ,  $p = 0.053$ ]. For the middle exposure group, percent commission errors across the three blocks were 33.3%, 39.2%, and 49.0% [block  $F(2,52) = 3.56$ ,  $p = 0.036$ ]. For the high-exposure group, percent commission errors across the three blocks were 33.8%, 46.3%, and 53.5% [block  $F(2,50) = 7.38$ ,  $p = 0.002$ ]. Between groups, dose-response analyses are shown in Figure 2A. Results revealed no significant association between PCB exposure and percent commission errors during block 1 (linear  $F(1,170) = 0.04$ ,  $p = 0.844$ ), a possible trend for association at block 2 [ $F(1,164) = 2.23$ ,  $p = 0.13$ ], and a significant linear association by block 3 [ $F(1,162) = 7.62$ ,  $p = 0.006$ ] (Figure 2A,B).

**DDE and MeHg.** Neither cord dichlorodiphenyldichloroethylene (DDE) nor hair MeHg met the statistical criterion for inclusion as covariates ( $p > 0.20$ ). Even if these variables were included as covariates, the outcome with PCBs was unchanged ( $p < 0.006$ ). If the analysis was restricted to include only those subjects with both behavioral data and valid (not missing) MeHg data, the sample size was reduced, but PCB results remained unchanged whether MeHg in the first half of pregnancy ( $n = 132$ ) was included ( $p = 0.007$ ), or MeHg in the second half of pregnancy ( $n = 125$ ) was included ( $p = 0.049$ ).



**Figure 1.** Sagittal MRI scan of exemplar subject brain. Areas measured volumetrically were genu (A), splenium (B), and cerebrum (C).

**Effect mediation.** In testing for effect mediation, testing block 3 was considered because that was the block in which the PCB association was most pronounced. Each of these variables was significantly related to performance (McCarthy General Cognitive Index,  $r^2 = 0.04$ ,  $p < 0.005$ ; failure to remain seated,  $r^2 = 0.04$ ,  $p < 0.005$ ; splenium,  $r^2 = 0.20$ ,  $p < 0.001$ ). No changes in the association between PCBs and percentage of errors of commission were produced when the variable McCarthy General Cognitive Index [ $F$  for change = 0.09, not significant], getting out of seat [ $F$  for change = 0.72, not significant], or splenium size [ $F$  for change = 0.67, not significant] were entered. Therefore, the PCB association was not mediated by these variables.

**Child satisfaction rating.** Subjects' responses on the five-point Likert (1 = extremely happy, 5 = extremely unhappy) scale were moderately and negatively correlated with percent correct on the CPT ( $r^2 = 0.057$ ,  $p = 0.001$ ) and positively related to errors of commission ( $r^2 = 0.025$ ,  $p < 0.05$ ). There was a trend for association between prenatal PCB exposure and ratings of less satisfaction with the task [linear  $F(1,178) = 3.06$ ,  $p = 0.082$ ], with the most exposed children tending to rate the task more negatively. Mean ratings for the four exposure groups

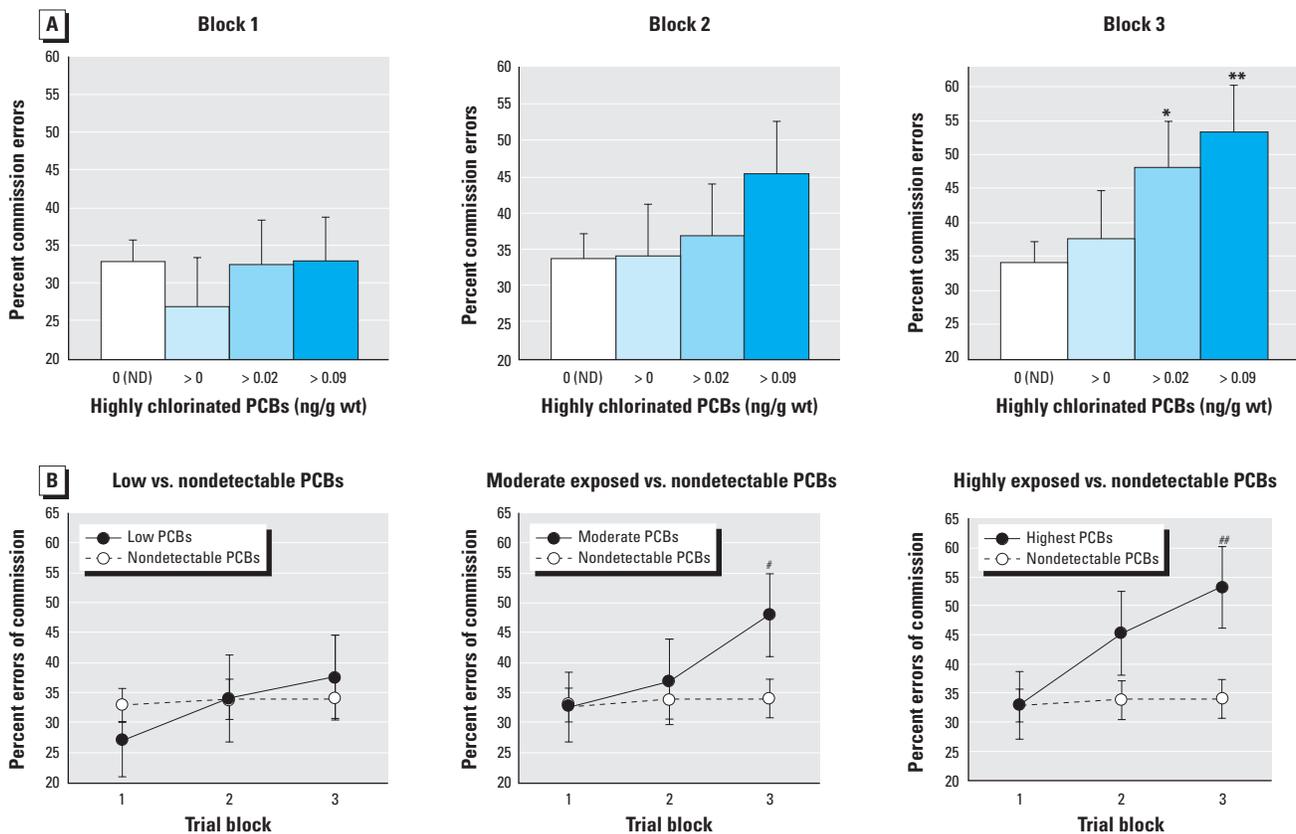
(from nondetectable to most exposed) were 2.07, 1.82, 2.14, and 2.67, respectively. MeHg met the statistical criterion for inclusion as a covariate in this analysis. Maternal hair MeHg was significantly related to child satisfaction ratings (mercury during first half of pregnancy,  $r^2 = 0.078$ ,  $p = 0.0005$ ; mercury during second half of pregnancy,  $r^2 = 0.044$ ,  $p = 0.009$ ), even after controlling for confounders. Higher maternal hair MeHg levels were associated with more negative satisfaction ratings by the children.

**MRI analyses ( $n = 60$  subjects).** MRI parameters. The mean, standard deviation, and range for the corpus callosum, genu, splenium, and total cerebral volume are shown in Table 4. Data are shown separately for children in the least exposed ( $n = 30$ ) and most exposed ( $n = 30$ ) children.

**Corpus callosum and CPT performance.** The relationships between volumetric brain parameters and CPT performance are shown in Table 5. The size of the splenium was the major predictor of errors of commission, with smaller splenium volumes associated with greater errors of commission. This finding was preserved even after controlling for demographic variables and after controlling for the size of the genu and splenium. The modest association between the genu and

omission errors was not significant after control for demographic variables (Table 5).

**The splenium as effect moderator.** In the subsample of children selected for the MRI study ( $n = 60$ ), the least exposed children ( $n = 30$ ) and most exposed children ( $n = 30$ ) differed on errors of commission ( $F = 5.0$ ,  $p = 0.030$ ), as expected given the association seen in the larger ( $n = 189$ ) sample. However, after control for confounders, PCBs were not related to splenium size [ $F(1,44) = 0.01$ ,  $p = 0.98$ ] (Table 4). Although the overall correlation between the splenium size and errors of commission was substantial and significant ( $r = -0.45$ ,  $p = 0.001$ ), the correlations between splenium size and performance within the least exposed and the most exposed children differed for each group: For the least exposed group,  $r = -0.27$  ( $p = 0.16$ ); for the most exposed,  $r = -0.65$  ( $p < 0.0009$ ). These two correlations differed significantly ( $p < 0.01$ ). These data show that the increase in errors of commission associated with smaller splenium size was much steeper in PCB-exposed children (Figure 3). In children with the smallest spleniums (bottom quartile), PCB-exposed children showed more than double the rate of commission errors compared with lesser exposed children. The strength of association between PCBs and percent commission errors



**Figure 2.** (A) Dose–response relationships between PCBs and commission errors across the three 4-min testing blocks. \* $p = 0.052$ ; \*\* $p = 0.008$ . (B) Within-group changes in commission errors across the three testing blocks. Left, children with nondetectable PCB levels versus those with low exposure; middle, nondetects versus moderate exposure; right, nondetects versus high exposure. # $p = 0.036$ ; ## $p = 0.002$ . Error bars represent SE.

was  $r^2 = 0.24$ , more than eight times the magnitude of the association seen when not taking the splenium into account. In contrast, no significant relationship between PCBs and errors of commission was observed in children with the largest spleniums ( $r^2 = 0.00$ ; Figure 3).

**Discussion**

The results of the present study support the hypothesis that response inhibition may be correlated with prenatal PCB exposure, even in the absence of a relationship with global cognition (Stewart et al. 2003). These findings are consistent with animal literature (Berger 2001; Lilienthal et al. 1990; Mele et al. 1986; Rice 1997). The present findings argue that the bias in PCB research toward global measures of cognition may result in a failure to uncover important relationships that have previously been untested. This observation is not novel, because concerns about sole reliance on global IQ as an end point in epidemiologic studies have been raised many times in the literature (e.g., Cohn and Cory-Slechta 1994; Rice 1996; Schantz 1996). The present data also demonstrate that measurement of neural structures that are strongly predictive of response inhibition may be critical to the interpretation of the relationships observed. At the very least, such data provide a powerful covariate, which may serve to markedly enhance the degree of statistical control in the analysis of response inhibition. Even more important, such data may serve as an effect moderator. In the case of the present report, the data indicated that children with the smallest spleniums were most vulnerable to the hypothesized effects of PCBs. Conversely, children with large spleniums and good response inhibition had no putative effects of PCBs to note.

**Dose-response and qualitative evidence.** Although statistical associations and  $p$ -values are a significant part of evaluating the reliability of the results in a study, their worth relies in large part on their ability to combine with other corroborative information to support the hypothesis under study (Thompson 1998). In investigations concerning PCBs or other toxicants, a dose-response relationship is considered an important component of the effect (Eaton and Klaassen 1996), providing corroborative evidence. In the present report, there was a fairly compelling and systematic

dose-response relationship between PCB exposure and errors of commission. The magnitude of the increase in errors of commission across the three testing blocks was directly proportional to the degree of exposure, with statistically significant differences from the control group beginning at the intermediate exposure group and increasing to the most exposed group. In addition, a statistical trend indicated that the most exposed children may have rated the task less satisfactorily compared with lesser exposed children. This is what one might predict given that higher errors of commission are associated with lower satisfaction ratings ( $r^2 = 0.025$ ,  $p < 0.05$ ).

Although PCBs were positively associated with errors of commission, the association emerged as a function of testing block. Post hoc testing following the significant PCB  $\times$  testing block interaction revealed no association at block 1, a possible trend for association at block 2, and a statistically significant and dose-dependent association by block 3. There are several plausible explanations for this pattern of data. First, vigilance is progressively taxed and the test may become more aversive or frustrating as it goes on. Indeed, the reduction in accuracy in responding across the 12-min task may reflect this. Second, performance earlier in the test may better reflect processes unrelated to response inhibition, including acclimation to the test. During block 2 and certainly by block 3, response inhibition, as opposed to other behavioral processes, is probably a much stronger contributor to performance. There is some evidence to support this contention. Early in the test, failure to remain seated was a much larger predictor of performance in block 1 than block 2 and especially block 3. Remaining seated is not a measure of response inhibition because much of it is a measure of test compliance. In contrast, the strongest predictors of response inhibition shown in Table 3, sex and splenium size, showed stronger relationships to performance in the latter testing blocks, especially testing block 3.

**Effect mediation versus moderation by the corpus callosum.** Of all the exposure and demographic variables measured in this study, splenium size was the single most important predictor of response inhibition. This association was not entirely unexpected, because the

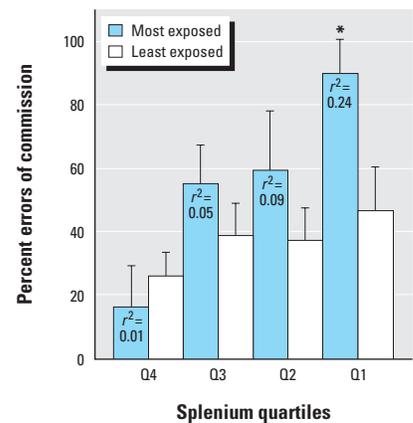
splenium and other structures in the corpus callosum have been found to be smaller in those with disorders that predict impaired response inhibition [e.g., ADHD (Hynd et al. 1991; Semrud-Clikeman et al. 1994)]. Whether the observed effect is truly due to a smaller splenium (fewer axons or axons with smaller diameters), less myelination, or associated changes in the areas that they connect (parietal, occipital, and temporal cortexes) is not yet known. It is interesting to note, however, that the cortical areas linked by the splenium play an important role in visual object recognition and discrimination (ventral/temporal visual pathway), as well as integrating what is observed with the proper motor response (dorsal/parietal visual pathway) (Deyoe et al. 1994; Ts'o and Roe 1995; Van Essen and DeYoe 1995). Presumably, these functions would be critical for a visual signal detection task such as the Catch-the-Cat test. It was thus reasonable to ask whether the splenium mediated or moderated the PCB effect, especially given that PCBs have been hypothesized to disrupt thyroid hormone (Porterfield and Hendry 1998), a hormone that plays a significant role in the development of the splenium (Hauser et al. 1997).

Effect mediation and moderation differ in that analysis of effect mediation asks whether PCBs influence behavior indirectly, through first affecting an intermediating variable (the splenium), which in turn causes the observed

**Table 5.** Correlations between volumetric brain measures and CPT performance.

Brain region	Commission errors	Omission errors
Genu	-0.001	+0.290*
Splenium	-0.486**	+0.010
Cerebrum	-0.058	+0.222

\* $p < 0.05$ ; \*\* $p < 0.001$ .



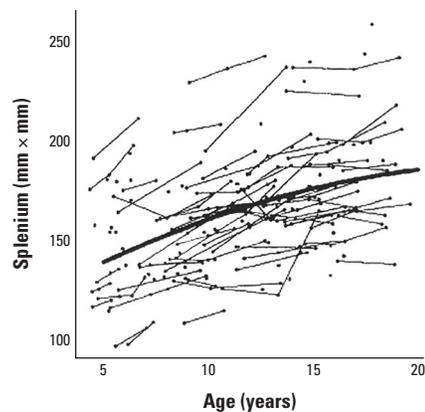
**Figure 3.** Relationship between cord PCB and errors of commission as a function of splenium volume. The x-axis plots the top quartile (Q4), upper interquartile (Q3), lower interquartile (Q2), and bottom quartile (Q1) of the splenium;  $r^2$  for PCB association with errors of commission. \* $p < 0.05$ .

**Table 4.** Volumetric brain parameters in least and highest exposed children.

Area scanned	PCB exposure level	Mean volume (mm <sup>2</sup> ) $\pm$ SD	Range
Corpus callosum	Low	431.57 $\pm$ 64.11	300.40–571.77
	High	438.60 $\pm$ 77.11	286.40–657.28
Genu	Low	121.33 $\pm$ 24.60	75.20–182.35
	High	125.04 $\pm$ 22.36	84.48–175.14
Splenium	Low	105.36 $\pm$ 26.40	48.52–179.99
	High	103.92 $\pm$ 26.51	48.80–163.02
Cerebrum	Low	7901.62 $\pm$ 864.23	6266.51–9958.15
	High	8018.04 $\pm$ 743.54	6656.28–9783.02

behavioral changes. This is one method to elucidate mechanism of effect. Effect mediation is most likely when there is some degree of association between PCBs and the mediator (splenium) and between PCBs and the outcome measure (errors of commission), and an association between the mediator and the outcome measure. In the present study, analysis for effect mediation indicated that the PCB association with response inhibition was not mediated through the splenium. PCBs were not significantly related to the splenium, and the  $F$ -ratio for association between PCBs and commission errors was not significantly changed by the presence or absence of splenium volumes as a covariate in the analysis. This argues that whatever the mechanism(s) underlying the PCB association with response inhibition, it is not caused by PCBs affecting the splenium of the corpus callosum.

In contrast to effect mediation, which deals with potential mechanisms, analysis of effect moderation asks whether an association is modified by a third variable. Put another way, regardless of the mechanism(s) of effect, are there other variables that enhance or suppress the association between two variables? In the present study, we found that the splenium acted as an effect moderator upon the PCB–response inhibition relationship. Specifically, the smaller the splenium size, the greater the vulnerability to the putative PCB-related impairment. For children with the largest spleniums (top quartile), the PCB association was not evident. The strength of the PCB association grew, however, as a function of reduced splenium size, and a very large PCB association was found in children with the smallest spleniums. This was not at all expected, and in fact we discovered this when we were attempting to demonstrate that the relationships were



**Figure 4.** Developmental trajectories of the splenium for 139 children 4.5–18 years old. Single dots represent single observations; lines connect repeated assessments for a single child. The thick line is the line of best fit. Note parallelism in the trajectories. Adapted from Giedd et al. (1999); reprinted with permission.

equivalent in both groups. One interpretation of these data is that children with larger spleniums have a greater proportion of neural processing dedicated to response inhibition, and therefore are highly resistant to factors that impair it; conversely, children with smaller spleniums have less central nervous system resources directed toward inhibition of responses and are more susceptible to those factors that promote impulsive responding.

This hypothesis gains some support when examining the relationship between response inhibition and its other major predictors. For example, next to the splenium, sex was the second strongest predictor of percent errors of commission ( $r^2 = 0.12$ ,  $p < 0.009$ ), with males making more errors of commission compared with females (56 vs. 30%, respectively). However, when examining the sex effect as a function of splenium size, the splenium was a large effect moderator. Similar to the association with PCBs, sex effects were most pronounced in children with the smallest spleniums (bottom quartile), with sex accounting for a large percentage ( $r^2 = 0.33$ ,  $p < 0.05$ ) of the variability (males averaged 84% commission errors; females averaged 41%). In contrast, no sex differences were observed in children with the largest (top quartile) spleniums ( $r^2 = 0.05$ , not significant). And, like the association with PCBs, effect sizes in children with splenium volumes in the interquartile ranges (middle two quartiles) fell between the effect sizes seen in the extremes. These data combined with the PCB data argue that the splenium plays a major role in predicting whether other factors that affect response inhibition will be manifest.

The difference between the age at which the MRI scans were taken and the age at which the behaviors were assessed is clearly an issue to consider when interpreting these findings. The MRI scans in the present report were obtained at approximately 7.8 years old, in an effort to examine the relationship between prenatal contaminants, behavioral development, and effect mediation by the corpus callosum. The behavioral data in the present report were collected 3.5 years before these MRI scans. There is good evidence, however, that the temporal incongruity between the MRI and behavioral assessments is largely inconsequential to the interpretation of the data. Although it is true that the volume of the corpus callosum changes dramatically between the ages of 4 and 8 years (Giedd et al. 1999), the relative size of the corpus callosum, and especially the splenium, between children is extremely stable across development. Evidence for this was provided by Giedd et al. (1999), who examined the development and stability of the corpus callosum from early childhood through the teen years. Figure 4 summarizes these data. The relative relationships between the volume

of the splenium at 4 years old remain almost perfectly intact when reassessed at 6 years old and then at 8 years old. Similar stability is seen at later stages of development. These data suggest that individual differences in splenium size across development are quite stable.

## Conclusions

The data reported in the present study provide evidence of a correlative relationship between prenatal PCB exposure and poorer response inhibition in children. These data are consistent with the rodent data (Berger 2001) and the small number of studies performed in nonhuman primates exposed to PCBs (Mele et al. 1986; Rice 1997, 1999a, 1999b). In the one other study where a paradigm identical to the present study was performed (Jacobson et al. 1992), there was some evidence of reduced performance on a composite score of a CPT, of which commission errors were a contributor. In the present report, the association between PCB levels and commission errors, although statistically significant, was small ( $r^2 = 0.03$ ). However, there is reasonable evidence that the size of this association is strongly modulated by intrinsic central nervous system structures that may normally serve to regulate response inhibition (e.g., the splenium). The evidence suggests that, in children with optimal development of these structures, the PCB association may be absent; conversely, in children with suboptimal development of these structures, the PCB association may be strong. Further work and independent replication are needed to confirm these findings.

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